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# Diagnosis of depth of invasion for early colorectal cancer using magnifying colonoscopy

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**Key words**
colon cancer, colorectal cancer, depth diagnosis, magnifying endoscopy, submucosal cancer.

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**Abbreviations:**
CRC, colorectal cancer; EMR, endoscopic mucosal resection; s.m., submucosal; s.m.-s., submucosal slight; s.m.-d., submucosal deep; LST-G, laterally spreading tumor granular type.

## Abstract

**Background and Aims:** Early colorectal cancer (CRC) with submucosal deep (s.m.-d.) invasion should not be treated with endoscopic mucosal resection due to the higher incidence of lymph-node metastasis. It is, therefore, clinically important to accurately diagnose s.m.-d. lesions before treatment.

**Methods:** We analyzed the endoscopic features, including pit patterns, of early CRC with s.m.-d. invasion observed using magnifying colonoscopy. We retrospectively investigated 379 cases of early CRC. Lesions were divided into three macroscopic subtypes (pedunculated type, sessile type and superficial type) based on endoscopic findings. Eight endoscopic factors were evaluated retrospectively for association with s.m. invasion and then compared to histopathological findings.

**Results:** The superficial type had a significantly higher frequency of s.m.-d. invasion (52.4% [77/147] vs 24.6% [14/57] and 39.4% [69/175], $P$-value < 0.05, respectively, for pedunculated and sessile types). Based on multivariate analysis, an independent risk factor for s.m.-d. invasion was the existence of an invasive pit pattern in sessile and superficial types (odds ratios of 52.74 and 209.67, respectively). Fullness was also an independent risk factor for s.m.-d. invasion in the superficial type (odds ratio = 9.25). There were no independent risk factors for s.m.-d. invasion in the pedunculated type.

**Conclusion:** High magnification pit pattern diagnosis proved to be useful for predicting s.m.-d. invasion in sessile and superficial types although it was not as helpful with the pedunculated type.

## Introduction

The incidence of colorectal cancer (CRC) has recently been increasing in Japan. Early CRC that consist of intramucosal cancers or submucosal (s.m.) cancers that only superficially invade the s.m. layer (s.m.-s.) can be removed by endoscopic mucosal resection (EMR).[1] Endoscopic treatment for early CRC is considered appropriate when the following conditions have been satisfied: a lesion is determined histopathologically to be well differentiated; invasion of the s.m. layer is < 1000 $\mu$m (s.m.-s.); and the lesion is negative for both lymphovascular invasion and sprouting.[2] Early CRC with s.m. deep (s.m.-d.) invasion should not be treated with EMR due to an increased risk of lymph-node (LN) metastasis, which has been reported to range from 6.9% to 22.2%.[2] Consequently, it is clinically important to accurately diagnose the depth of invasion before treatment.

A role for magnifying endoscopy in the colon has previously been indicated for the diagnosis of flat and depressed lesions, identification of dysplasia in ulcerative colitis, discrimination among polyp types and assessing the completeness of EMR.[3–5] Pit pattern classification for colonic lesions has also been well documented in the past. We have already reported that pit pattern analysis using magnification colonoscopy was useful in the diagnosis of invasive depth in early CRC, particularly flat and depressed lesions.[6–9] No studies have been reported as yet, however, that focused on the diagnosis of s.m. invasion in pedunculated and sessile type lesions.

The aim of this study was to analyze the endoscopic features (including pit patterns) of early CRC with s.m.-d. invasion from a large number of early CRC including pedunculated and sessile types using magnifying colonoscopy in order to determine the appropriate therapeutic strategy.

## Methods

A total of 844 early CRC were resected endoscopically or surgically at the National Cancer Center Hospital in Tokyo between October 1998 and September 2005. In this series, 687 lesions were removed by endoscopic resection and 157 underwent surgical treatment. All lesions were examined using magnifying colonoscopy before treatment. Among them, 232 tumors were positive for s.m. invasion (612 intramucosal cancer lesions, 52 s.m.-s. lesions

and 180 s.m.-d. lesions). We also investigated the 256 consecutive intramucosal early CRC that were resected between January 2004 and September 2005 as our control group (EMR, 253 lesions; and surgery, three lesions) to help ascertain and evaluate differences between intramucosal and s.m. invasive cancers. From this total of 488 early colorectal lesions, 68 (13.9%) were excluded because the quality of their magnifying colonoscopy pictures was too poor for an accurate assessment either because of mucous or the pictures were out of focus leaving 420 (86.1%) lesions with suitable pictures for s.m. invasion diagnostic purposes. In addition, granular type laterally spreading tumors (LST-G) consist of several different shapes. For example, some LST-G have a flat elevated component surrounding a large nodule. It is therefore difficult to categorize such lesions as being either the protruded or flat type.[10,11] Accordingly, 41 LST-G were excluded from this study. Eventually, a total of 379 lesions were analyzed retrospectively (179 intramucosal lesions, 40 s.m.-s. lesions and 160 s.m.-d. lesions). These lesions were then divided into three subtypes according to the Paris classification: pedunculated type (type 0-Ip), sessile type (type 0-Is) and superficial type, which included slightly elevated (0-IIa), completely flat (0-IIb) and slightly depressed lesions without ulcer (0-IIc).[13]

## Endoscopic examination

In our medical facility, all colonoscopies are performed with magnification. When a lesion was detected by conventional endoscopic examination, surface mucin was washed away with lukewarm water containing pronase (Pronase MS, Kaken Pharmaceutical, Tokyo, Japan) and then 0.4% indigo-carmine dye was sprayed over the lesion in order to enhance its surface detail. High magnification colonoscopes (CF-240ZI, PCF-240ZI and CF-200Z, Olympus Optical, Tokyo, Japan) were also used in this study. When a high magnification observation with indigo-carmine dye was not enough to determine the surface structure (pit pattern analysis), staining was added with 0.05% crystal violet.[14] The additional time usually needed to complete the magnification observation was less than 10 min including 30 s to one minute to wash the lesion, one minute for crystal violet staining and one to five minutes for the actual observation.

The depth of tumor invasion was classified as intramucosal, s.m.-s. (invasion $< 1000$ μm from the muscularis mucosa) and s.m.-d. (invasion $\geq 1000$ μm from the muscularis mucosa). In order to elucidate the possible association between s.m.-d. invasion and various endoscopic findings, we selected eight endoscopic factors related to s.m. deep invasion from previously published literature[10–12] and then those eight endoscopic factors were investigated retrospectively.

1 Tumor Size—receiver operating characteristic (ROC) curves were used to determine the relationship between tumor size cut-offs and diagnostic accuracy. Based on these ROC curves, we chose tumor size cut-offs for pedunculated (20 mm), sessile (15 mm) and superficial (10 mm) tumors. The size for en bloc resected specimens was estimated by histopathological examination and for piecemeal resected specimens by reviewing endoscopic photographs.
2 Loss of Lobulation—with or without a loss of lobulation (Fig. 1).

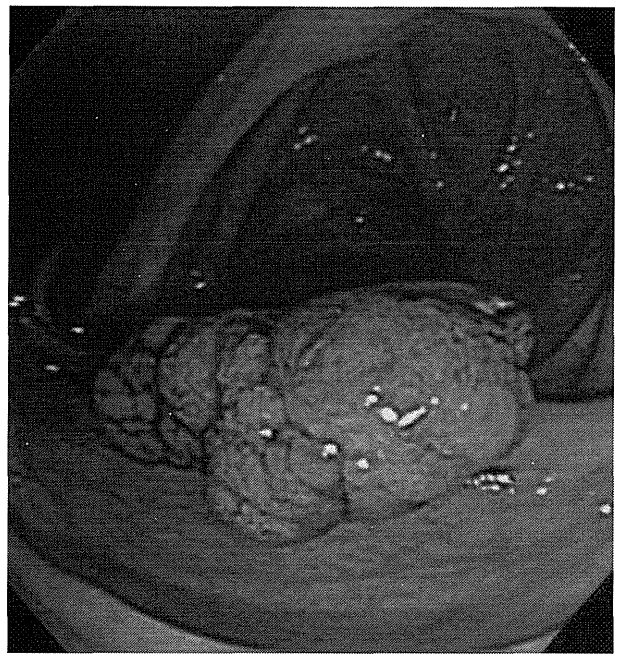

**Figure 1** Loss of lobulation.

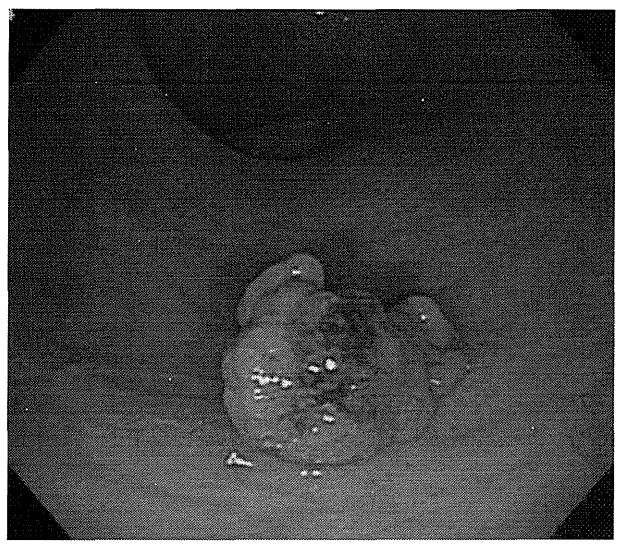

**Figure 2** Excavation.

3 Excavation—a crumbled, damaged area of the tumor that prevents observation of the surface structure (Fig. 2).
4 Demarcated Depressed Area—with or without such a demarcation (Fig. 3).
5 Stalk Swelling—a thickened and expanded stalk (Fig. 4).
6 Fullness—a bursting appearance due to expansive growth of the tumor (Fig. 5).
7 Fold Convergency—a fold convergency towards the tumor (Fig. 6).

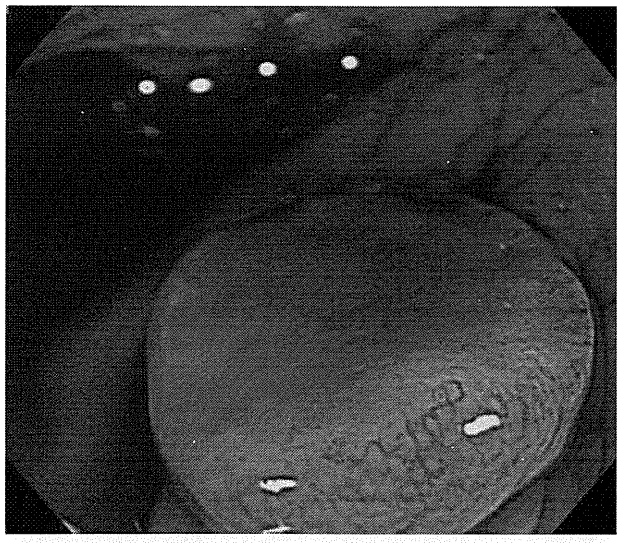

**Figure 3** Demarcated depressed area.

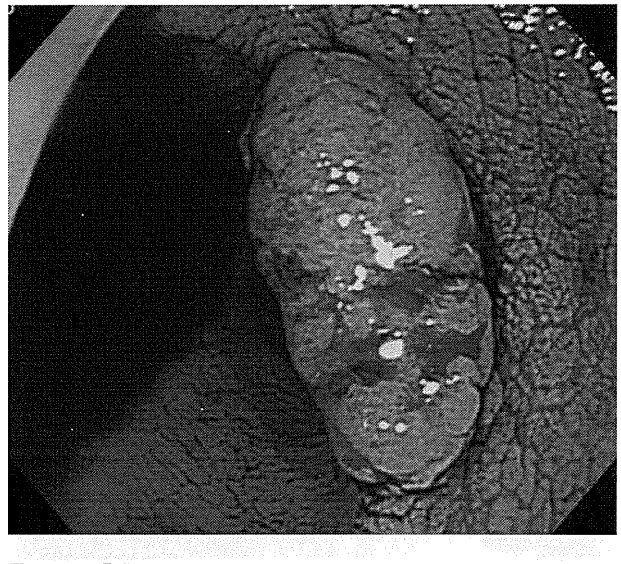

**Figure 5** Fullness.

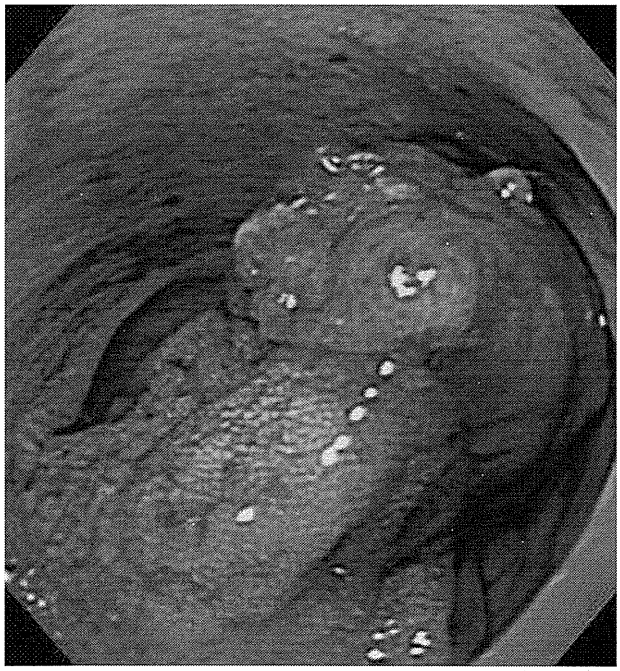

**Figure 4** Stalk swelling.

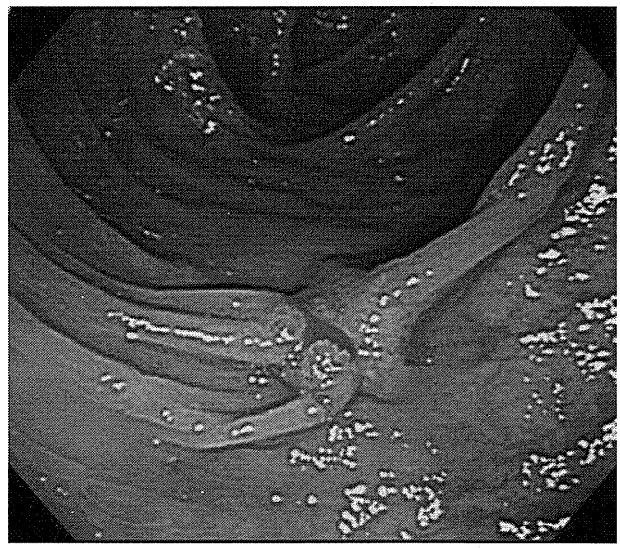

**Figure 6** Fold convergency.

8 Pit Pattern—'Invasive pattern' or 'Non-invasive pattern' with the 'Invasive pattern' characterized by irregular and distorted epithelial crests observed in a demarcated area suggesting s.m.-d. invasion $\geq 1000\ \mu m$ while the 'Non-invasive pattern' did not have those two findings that suggested intramucosal neoplasia or s.m.-s. invasion $< 1000\ \mu m$ (Fig. 7a,b).[2,3,15]

Different endoscopic factors were assessed for each type. 'Stalk Swelling' was assessed for only the pedunculated type; 'Loss of Lobulation' and 'Excavation' were assessed for the pedunculated and sessile types; 'Fullness' and 'Fold Convergency' were assessed for the superficial type; and 'Size', 'Demarcated Depressed Area' and 'Pit Pattern' were assessed for all three types.

All endoscopic factors were determined retrospectively by three highly experienced endoscopists (H. I., Y. S. and T. M.) each of whom had previously performed over 1000 colonoscopies each year for more than five years. Final determination of endoscopic findings was decided by agreement of at least two of the three endoscopists. The relationships between the various endoscopic factors and the extent of s.m.-d. invasion were analyzed histopathologically in those lesions with s.m.-d. invasion.

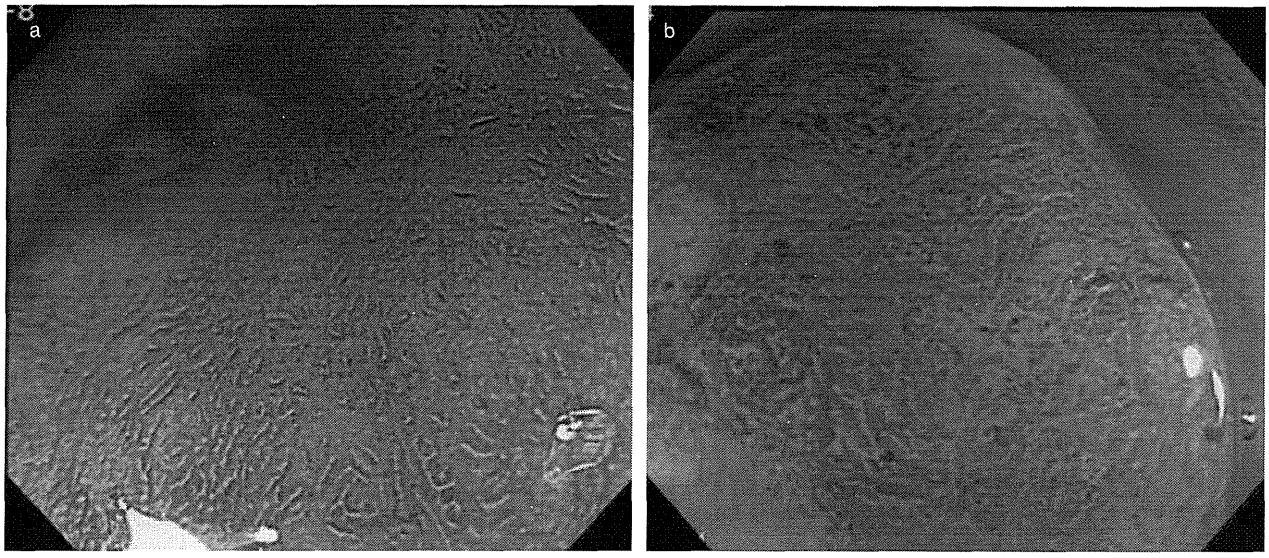


**Figure 7** (a) Non-invasive pattern. (b) Invasive pattern.

**Table 1** Clinicopathological characteristics of lesions

| | Pedunculated type | Sessile type | Superficial type |
|---|---|---|---|
| Number of lesions | 57 | 175 | 147 |
| Tumor size (mean ± SD) | 17.2 ± 6.5 mm | 16.5 ± 8.5 mm | 16.3 ± 8.6 mm |
| Histopathological diagnosis | | | |
| Intramucosal cancer | 37 | 98 | 44 |
| s.m.-s. (< 1000 μm) | 6 | 8 | 26 |
| s.m.-d. (≥ 1000 μm) | 14 (24.6%) | 69 (39.4%) | 77 (52.4%) |
| Distribution | | | |
| Right colon | 9 (15.8%) | 43 (24.6%) | 58 (39.5%) |
| Left colon | 44 (77.2%) | 60 (34.3%) | 41 (27.9%) |
| Rectum | 4 (7.0%) | 72 (41.1%) | 48 (32.6%) |

SD, standard deviation; s.m.-d., submucosal deep invasion; s.m.-s., submucosal superficial invasion.

### Histopathology

Resected specimens were fixed in a 10% buffered formalin solution, embedded on paraffin and then cut into 2–3 mm slices. Each section was stained with hematoxylin–eosin and then histopathologically diagnosed by a highly experienced pathologist. Histopathological diagnosis was based on the Vienna classification.[16] A microscope with a built-in ruler was used to determine the depth of s.m. invasion.

### Statistical analysis

Among the three macroscopic subtypes, the proportion of s.m. invasion was compared using the $\chi^2$-test. When characteristics showed a significant difference, we performed logistic regression including all such characteristics as part of the model. Statistical analyses were done with the SPSS 11.0 for Windows software package (SPSS, Chicago, IL, USA). Each test was two-sided and a $P$-value < 0.05 was defined as being statistically significant.

## Results

### Clinicopathological characteristics

Table 1 shows the clinicopathological characteristics of the early CRC examined in this study. The superficial type had a significantly higher frequency of s.m.-d. invasion compared to the pedunculated and sessile types (52.4% [77/147] vs 24.6% [14/57] and 39.4% [69/175], respectively). The pedunculated type was most commonly diagnosed in the left colon (77.2% [44/57]) in contrast to the sessile and superficial types, which were most commonly diagnosed in the rectum (41.1% [72/175]) and the right colon (39.5% [58/147]), respectively.

### Endoscopic factors for submucosal deep invasion

In the pedunculated type, a larger tumor size (≥ 20 mm), loss of lobulation, excavation, the presence of an invasive pit pattern and

**Table 2** Relationship between endoscopic factors and submucosal deep invasion in 57 pedunculated type lesions

| | | s.m.-d. ca./*n* | Univariate analysis | Multivariate analysis (includes pit pattern) | | |
|---|---|---|---|---|---|---|
| | | | *P*-value | Odds ratio | 95% CI | *P*-value |
| Size | ≥ 20 mm | 10/22 | < 0.01 | 1.49 | 0.22–10.31 | 0.69 |
| | < 20 mm | 4/35 | | | | |
| Loss of lobulation | Present | 12/28 | < 0.01 | 3.15 | 0.47–21.01 | 0.24 |
| | Absent | 2/29 | | | | |
| Excavation | Present | 7/11 | < 0.001 | 2.52 | 0.36–17.47 | 0.35 |
| | Absent | 7/46 | | | | |
| Demarcated depressed area | Present | 2/4 | 0.25 | ND | ND | ND |
| | Absent | 12/53 | | | | |
| Pit pattern | Invasive | 7/9 | < 0.0001 | 4.62 | 0.50–42.98 | 0.18 |
| | Non-invasive | 7/48 | | | | |
| Stalk swelling | Present | 9/19 | < 0.01 | 2.00 | 0.40–10.10 | 0.40 |
| | Absent | 5/38 | | | | |

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

**Table 3** Relationship between endoscopic factors and submucosal deep invasion in 175 sessile type lesions

| | | s.m.-d. ca./*n* | Univariate analysis | Multivariate analysis (includes pit pattern) | | |
|---|---|---|---|---|---|---|
| | | | *P*-value | Odds ratio | 95% CI | *P*-value |
| Size | ≥ 15 mm | 53/96 | < 0.0001 | 1.86 | 0.61–5.66 | 0.28 |
| | < 15 mm | 16/79 | | | | |
| Loss of lobulation | Present | 63/92 | < 0.0001 | 5.99 | 1.76–20.42 | < 0.01 |
| | Absent | 6/83 | | | | |
| Excavation | Present | 42/57 | < 0.0001 | 1.51 | 0.45–5.05 | 0.50 |
| | Absent | 27/118 | | | | |
| Demarcated depressed area | Present | 19/29 | < 0.01 | 0.20 | 0.03–1.44 | 0.11 |
| | Absent | 50/146 | | | | |
| Pit pattern | Invasive | 55/61 | < 0.0001 | 52.74 | 10.89–255.33 | < 0.0001 |
| | Non-invasive | 14/114 | | | | |

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

swelling of the stalk were each significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, however, there was no independent risk factor for s.m.-d. invasion (Table 2).

In the sessile type, the presence of a larger tumor size (≥ 15 mm), loss of lobulation, excavation, a demarcated depressed area and an invasive pit pattern were each significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, the independent risk factors for s.m.-d. invasion were loss of lobulation and the existence of an invasive pit pattern ($P < 0.01$, odds ratio = 5.99; and $P < 0.0001$, odds ratio = 52.74, respectively) (Table 3).

In the superficial type, fullness, fold convergency, a demarcated depressed area and an invasive pit pattern were significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, the independent risk factors for s.m.-d. invasion were the existence of fullness and an invasive pit pattern ($P < 0.01$, odds ratio = 9.25; and $P < 0.0001$, odds ratio = 209.67, respectively) (Table 4).

## Pit pattern analysis

The clinical classification of pit patterns has proven to be effective in differentiating intramucosal or s.m.-s. invasion < 1000 μm from s.m.-d. invasion (≥ 1000 μm). The calculated sensitivity, specificity, positive predictive value, negative predictive value and accuracy are shown in Table 5. The overall accuracy for differentiating intramucosal or s.m.-s. invasion from s.m.-d. invasion was 84.2% in the pedunculated type, 88.6% in the sessile type and 92.5% in the superficial type. The diagnostic accuracy of the invasive pit pattern was lower for pedunculated type lesions than for the other two macroscopic subtypes.

## Number of endoscopic factors analysis

Diagnostic accuracy based on the number of positive endoscopic factors observed during conventional endoscopy performed without magnification is shown in Table 6. When a particular lesion included four or more such endoscopic factors, overall accuracy was highest for the pedunculated type (86.0%). As for both the sessile and superficial types, however, overall accuracies of 81.1% and 80.3%, respectively, were highest when a particular lesion included two or more of the endoscopic factors.

**Table 4** Relationship between endoscopic factors and submucosal deep invasion in 147 superficial type lesions

| | | s.m.-d. ca./n | Univariate analysis | Multivariate analysis (includes pit pattern) | | |
|---|---|---|---|---|---|---|
| | | | *P*-value | Odds ratio | 95% CI | *P*-value |
| Size | ≥ 10 mm | 68/123 | 0.11 | ND | ND | ND |
| | < 10 mm | 9/24 | | | | |
| Fullness | Present | 66/86 | < 0.0001 | 9.25 | 2.14–40.00 | < 0.01 |
| | Absent | 11/61 | | | | |
| Fold convergency | Present | 38/50 | < 0.0001 | 1.99 | 0.50–7.97 | 0.33 |
| | Absent | 39/97 | | | | |
| Demarcated depressed area | Present | 52/68 | < 0.0001 | 1.92 | 0.45–8.15 | 0.37 |
| | Absent | 25/79 | | | | |
| Pit pattern | Invasive | 76/86 | < 0.0001 | 209.67 | 23.05–1907.48 | < 0.0001 |
| | Non-invasive | 1/61 | | | | |

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

**Table 5** Diagnostic analysis of invasive pit pattern by macroscopic type

| | Macroscopic type | | |
|---|---|---|---|
| | Pedunculated type | Sessile type | Superficial type |
| Sensitivity | 50.0% | 79.7% | 98.7% |
| Specificity | 95.3% | 94.3% | 85.7% |
| PPV | 77.8% | 90.2% | 88.4% |
| NPV | 85.4% | 87.7% | 98.4% |
| Overall Accuracy | 84.2% | 88.6% | 92.5% |

The $\chi^2$-test evaluates differences in sensitivity and there were significant differences among all three groups ($P < 0.05$).
NPV, negative predictive value; PPV, positive predictive value.

# Discussion

## Diagnosis of submucosal deep invasive cancer

We investigated various endoscopic factors including high magnification diagnosis of pit patterns in order to evaluate the predictive factors for s.m.-d. invasion in three macroscopic subtypes of early CRC. A higher incidence of s.m.-d. invasion in the superficial type and a difference in the diagnostic accuracy for predicting s.m.-d. invasion between the pedunculated type and the other two macroscopic types were found in our study.

In the superficial type, fullness and existence of the invasive pit pattern were independent risk factors for s.m.-d. invasion. Yokota *et al.* reported that conventional endoscopic findings were subjective,[12] however, fullness may not be a universal factor for determining s.m.-d. deep invasion. In the sessile type, multivariate analysis showed that loss of lobulation and existence of the invasive pit pattern were each independent risk factors for s.m.-d. invasion. A total of 68 lesions were excluded because of the poor quality of their magnifying colonoscopy pictures, however, so there could very well be a bias towards better pit pattern diagnostic analysis results in this study for both the superficial and sessile types.

In the pedunculated type, we were unable to demonstrate any independent endoscopic factors despite using pit pattern analysis. In addition, a combination of factors in pedunculated type lesions examined without magnification indicated that size and stalk swelling together had the same degree of overall diagnostic accuracy as produced by an analysis of invasive pit pattern using magnification. These results indicated that it is difficult to estimate the depth of tumor invasion in pedunculated type lesions using current magnification methods.

## Endoscopic diagnosis versus non-lifting sign

In previous studies, Uno *et al.* reported the clinical usefulness of the non-lifting sign to predict the depth of invasion prior to EMR for early CRC.[17] In addition, Ishiguro *et al.* classified s.m. extension of early colorectal cancer as s.m.1 (infiltration into the upper third of the s.m. layer), s.m.2 (middle third) or s.m.3 (lower third) according to the vertical level of s.m. invasion. They reported that the non-lifting sign indicated s.m.3 invasion had a sensitivity of 100% and a specificity of 83% although only 30.4% of s.m.2 cancers were non-lifting sign positive in their study.[18]

Our group reported that the sensitivity, specificity and accuracy of the non-lifting sign (61.5%, 98.4% and 94.8%, respectively) were insufficient in comparison with endoscopic diagnosis of invasion depth (84.6%, 98.8% and 97.4%, respectively).[19] Given these results, magnifying colonoscopy can be considered more effective than the non-lifting sign in distinguishing s.m.-d. invasive cancer based on the techniques and methods used in this study.

## Magnifying colonoscopy versus endoscopic ultrasonography

We previously reported that high magnification colonoscopy was superior to endoscopic ultrasonography (EUS) for the determination of invasion depth in early CRC.[13] In contrast, Hurlstone *et al.* demonstrated the superiority of EUS mini-probe staging over magnification colonoscopy.[20] At the present time, it is unclear whether magnification colonoscopy or EUS is superior for staging purposes. There is a learning curve associated with both modalities so the results can be influenced by the skill and experience of the endoscopist performing the procedure.

## Magnifying endoscopy

We routinely use magnifying colonoscopy because a magnifying endoscope enables standard conventional observations, but can

**Table 6** Diagnostic analysis according to number of positive endoscopic factors

| | | Number of positive endoscopic factors | | | | |
|---|---|---|---|---|---|---|
| | | ≥ 1 | ≥ 2 | ≥ 3 | ≥ 4 | ≥ 5 |
| Pedunculated type | Sensitivity | 92.7% | 71.4% | 64.3% | 42.7% | 14.3% |
| | Specificity | 44.2% | 67.4% | 86.1% | 100% | 100% |
| | PPV | 35.1% | 41.7% | 60.0% | 100% | 100% |
| | NPV | 95.0% | 87.9% | 88.1% | 84.3% | 78.2% |
| | Overall accuracy | 56.1% | 68.4% | 80.7% | 86.0% | 79.0% |
| Sessile type | Sensitivity | 97.1% | 87.0% | 52.2% | 13.0% | ND |
| | Specificity | 46.2% | 77.4% | 90.6% | 99.1% | ND |
| | PPV | 54.0% | 71.4% | 78.3% | 90.0% | ND |
| | NPV | 96.1% | 90.1% | 74.4% | 63.4% | ND |
| | Overall accuracy | 66.3% | 81.1% | 75.4% | 65.1% | ND |
| Superficial type | Sensitivity | 100% | 87.0% | 45.5% | 1.3% | ND |
| | Specificity | 34.3% | 72.9% | 91.4% | 100% | ND |
| | PPV | 62.6% | 77.9% | 85.4% | 100% | ND |
| | NPV | 100% | 83.6% | 60.4% | 48.0% | ND |
| | Overall accuracy | 68.7% | 80.3% | 67.4% | 48.3% | ND |

ND, no data; NPV, negative predictive value; PPV, positive predictive value.

also provide images from low to high magnification using a one-touch operational system. It is possible to distinguish between non-neoplastic and neoplastic lesions and estimate depth of tumor invasion in less than 10 minutes. The insertion technique and manipulation of the magnifying endoscope also are similar to those of a conventional endoscope during colonoscopy.[21,22]

### Treatment strategy

In considering therapeutic strategies, EMR should be the first-line treatment for intramucosal and s.m.-s. early CRC because it is less invasive. LN metastasis is more frequently present in s.m.-d. invasive cancer,[23,24] however, so we should avoid EMR for s.m.-d. invasive cancer because histopathological assessment is more difficult. In addition, incomplete EMR is thought to cause accelerated growth of any residual cancer and is also considered to be a positive risk factor for distant metastasis.[25,26] Recognizing the importance of reported endoscopic factors for predicting s.m.-d. invasion therefore is essential in determining the proper treatment choice in any given case.

For sessile and superficial type lesions endoscopically diagnosed as having an invasive pit pattern, a high percentage of cases revealed invasive cancer, particularly s.m.-d. cancer, so surgical resection is undoubtedly the appropriate treatment. Those lesions endoscopically diagnosed as having a non-invasive pattern, however, were mostly limited to the intramucosal layer, which makes EMR feasible. It is also technically possible now to remove large superficial lesions using the more recently developed endoscopic submucosal dissection procedure.[27–30]

In the pedunculated type, it is difficult to accurately estimate the depth of s.m.-d. invasion prior to endoscopic treatment, but the endoscopic resection of a pedunculated polyp is relatively easy from a technical point of view. It is recommended therefore that a pedunculated type lesion first be removed endoscopically followed by a histopathological determination of the depth of invasion. A surgical resection should then be performed when stalk invasion or lymph-vessel involvement has been revealed histopathologically.

### Limitations

This was a retrospective study conducted in a single center so the results need to be confirmed in a prospective multi-center trial. In addition, only pedunculated, sessile and superficial lesion macroscopic subtypes were included in this study.

## Conclusion

Pit pattern high magnification diagnosis proved to be useful for predicting s.m.-d. invasion in sessile and superficial type lesions, although it was not helpful with the pedunculated type. Consequently, diagnostic endoscopic treatment is advisable for pedunculated early CRC.

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# Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection

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**Abstract**
*Background and Aims* Endoscopic submucosal dissection (ESD) has recently been applied to the treatment of superficial colorectal cancer. Clinical outcomes compared with conventional endoscopic mucosal resection (EMR) have not been determined so our aim was to compare the effectiveness of ESD with conventional EMR for colorectal tumors ≥20 mm.
*Methods* This was a retrospective case-controlled study performed at the National Cancer Center Hospital in Tokyo, Japan involving 373 colorectal tumors ≥20 mm determined histologically to be curative resections. Data acquisition was from a prospectively completed database. We evaluated histology, tumor size, procedure time, en bloc resection rate, recurrence rate, and associated complications for both the ESD and EMR groups.
*Results* A total of 145 colorectal tumors were treated by ESD and another 228 were treated by EMR. ESD was associated with a longer procedure time (108 ± 71 min/29 ± 25 min; $p < 0.0001$), higher en bloc resection rate (84%/33%; $p < 0.0001$) and larger resected specimens (37 ± 14 mm/28 ± 8 mm; $p = 0.0006$), but involved a similar percentage of cancers (69%/66%; $p$ = NS). There were three (2%) recurrences in the ESD group and 33 (14%) in the EMR group requiring additional EMR ($p < 0.0001$). The perforation rate was 6.2% (9) in the ESD group and 1.3% (3) in the EMR group ($p$ = NS) with delayed bleeding occurring in 1.4% (2) and 3.1% (7) of the procedures ($p$ = NS), respectively, as all complications were effectively treated endoscopically.
*Conclusions* Despite its longer procedure time and higher perforation rate, ESD resulted in higher en bloc resection and curative rates compared with EMR and all ESD perforations were successfully managed by conservative endoscopic treatment.

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**Keywords** Endoscopic submucosal dissection (ESD) · Endoscopic mucosal resection (EMR) · Recurrence · Colon · Colorectal · Short-term clinical outcome

**Abbreviations**

| | |
|---|---|
| B-knife | Bipolar needle knife |
| $CO_2$ | Carbon dioxide |
| EMR | Endoscopic mucosal resection |
| EPMR | Endoscopic piecemeal mucosal resection |
| ESD | Endoscopic submucosal dissection |
| IT knife | Insulation-tipped knife |
| LN | Lymph node |
| sm | Submucosal |
| LST | Laterally spreading tumor |
| LST-G | Laterally spreading tumor granular type |
| LST-NG | Laterally spreading tumor nongranular type |
| NS | Not significant |
| SD | Standard deviation |
| sm1 | Minute submucosal cancer |
| sm2 | Submucosal deep cancer |

Endoscopic mucosal resection (EMR) is indicated for the treatment of superficial, early-stage colorectal cancer because of its minimal invasiveness and excellent results in terms of clinical outcomes [1–6]. However, conventional EMR techniques [6–8] currently used for the resection of laterally spreading tumors (LSTs) [7–10] are inadequate for the en bloc resection of flat lesions ≥20 mm because of both incomplete removal [11] and problems with local recurrence [12]. The endoscopic submucosal dissection (ESD) technique, which facilitates en bloc resection of early gastric cancer [11, 13–17], has recently been reported to be useful in the treatment of superficial colorectal tumors [18–28]. Previously, we reported on the effectiveness and safety of ESD for colorectal tumors using a bipolar needle knife (B-knife) (XEMEX Co., Tokyo, Japan) and an insulation-tipped knife (IT knife) (Olympus Optical Co., Ltd., Tokyo, Japan), neither of which produces any coagulation effect at the needle tip [20, 21, 24]. The effectiveness and long-term clinical outcome of ESD compared with conventional EMR is unclear, however, so the purpose of this study was to demonstrate the comparative effectiveness of ESD with conventional EMR for colorectal tumors ≥20 mm

## Materials and methods

Originally, 553 large (≥20 mm) colorectal tumors were resected endoscopically between January 2003 and December 2006 at the National Cancer Center Hospital (NCCH) in Tokyo with data acquisition from a prospectively completed database. Twenty-nine lesions that required surgery after endoscopic treatment because of noncurative resections and 151 lesions treated by conventional EMR for which follow-up colonoscopy examinations could not be carried out or ascertained at NCCH were excluded, leaving a final total of 373 large colorectal tumors that were included in this retrospective case-controlled study (Fig. 1). All ESD and EMR procedures were conducted by experienced colonoscopists (three staff doctors and two senior residents), each of whom had performed more than 1,000 colonoscopies annually.

The histology, tumor size, procedure time, en bloc resection rate, recurrence rate, and associated complications were evaluated for both an ESD group and a conventional EMR group. We defined an en bloc resection as a one-piece resection of the entire lesion as observed endoscopically. In assessing for a local recurrence or the presence of a residual tumor, we repeated colonoscopy

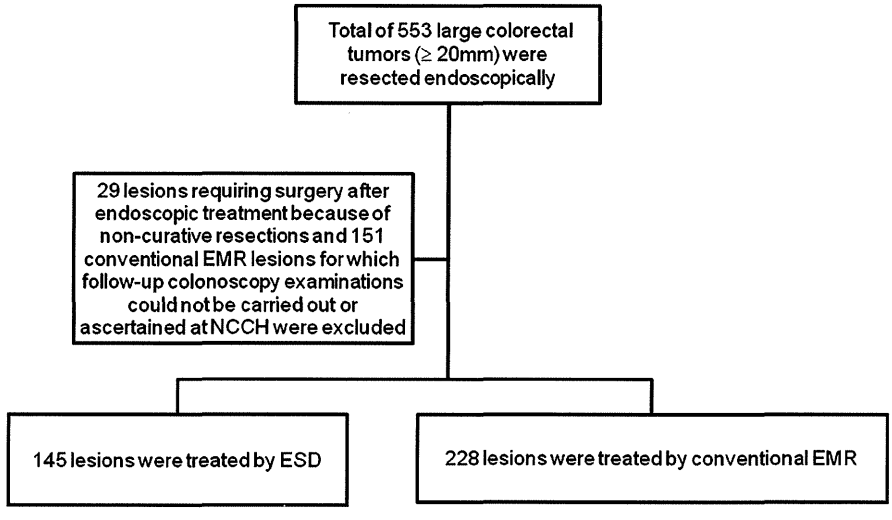


**Fig. 1** Flow chart showing the patients in this study

examinations at intervals of 6 months. The procedure time was measured from the injection of a submucosal (sm) injection solution into the sm layer to removal of the colonoscope after the resection of a tumor.

### Indication criteria for EMR and ESD

The existence of a noninvasive pattern [10, 24, 29–31] as determined by magnification chromoendoscopy was the minimum requirement for all lesions that were candidates for ESD and EMR. When a lesion was detected by conventional endoscopic examination, surface mucous was washed away with lukewarm water that contained pronase (Pronase MS; Kaken Pharmaceutical Co., Ltd., Tokyo, Japan) and then 0.4% indigo-carmine dye was sprayed over the lesion to enhance its surface detail. High-magnification colonoscopes (CF-240ZI, PCF-240ZI and H260AZI; Olympus Optical Co., Ltd.) were used to evaluate the surface character to differentiate an invasive pattern from a noninvasive pattern. The invasive pattern is characterized by irregular and distorted epithelial crests observed in a demarcated area suggesting that sm invasion is ≥1,000 μm while a noninvasive pattern does not have this finding which suggests intramucosal neoplasia or sm invasion <1,000 μm. When high-magnification observation with indigo-carmine dye was insufficient to determine the surface structure, we performed staining with 0.05% crystal violet. Based on extensive clinicopathological analyses [10], we defined the indications for ESD [24] as an LST nongranular (LST-NG)-type lesion >20 mm and an LST granular (LST-G)-type lesion >40 mm because they both had a higher sm invasion rate and were difficult to treat even by endoscopic piecemeal mucosal resection (EPMR) [7]. Some colonoscopists chose to perform EPMR [7] to treat LST-G lesions measuring between 20 and 40 mm with the final decision based on each individual colonoscopist's judgment. Large villous tumors as well as intramucosal lesions, recurrent lesions, and residual intramucosal lesions showing nonlifting sign after EMR were also potential candidates for ESD with the final decision once again made by each colonoscopist (Table 1).

### Endoscopic operating systems

ESD and EMR procedures were performed using Olympus PCF-Q240ZI, CF-Q240ZI, and CF-H260AZI video endoscopes.

### Bowel preparation

Bowel preparation consisted of a patient drinking 2–3 L of polyethylene glycol (PEG) solution in the morning before the procedure. In an effort to further ensure excellent bowel preparation, stool color was assessed before each colonoscopy by a trained nurse and additional PEG solution was used when necessary.

### ESD procedures

The procedures were primarily performed using a B-knife [20] or an IT knife with carbon dioxide ($CO_2$) insufflation instead of air insufflation to reduce patient discomfort [21]. Lesion margins were delineated before ESD using 0.4% indigo-carmine dye spraying (Fig. 2A, B). Following injection of Glyceol® (Chugai Pharmaceutical Co., Tokyo, Japan) (10% glycerol and 5% fructose in normal saline solution) [32] and sodium hyaluronate acid into the sm layer [33], a circumferential incision was made using the B-knife and an ESD was then carried out using both the B-knife and IT knife (Fig. 2C–F).

### Conventional EMR procedures

Conventional EMR procedures were performed using the inject and cut technique with a single-channel colonoscope (PCF-Q240ZI, CF-Q240ZI or CF-H260AZI; Olympus) and

**Table 1** Indication criteria for endoscopic submucosal dissection (ESD)/endoscopic mucosal resection (EMR)

| |
|---|
| *Minimum requirement* |
| A noninvasive pattern as determined by magnification chromoendoscopy was required for all lesions that were candidates for ESD and EMR |
| *Definite indication for ESD* |
| LST-NG lesion ≥20 mm |
| *Relative indication for ESD* |
| LST-G lesion ≥40 mm |
| Large villous tumor, intramucosal lesion, recurrent lesion or residual intramucosal lesion showing nonlifting sign after EMR |
| *Definite indication for EMR/EPMR* |
| Any lesion <20 mm |
| LST-G lesion ≥20 mm and <40 mm |

*EMR* endoscopic mucosal resection; *EPMR* endoscopic piecemeal mucosal resection; *ESD* endoscopic submucosal dissection; *LST-G* laterally spreading tumor granular type; *LST-NG* laterally spreading tumor nongranular type

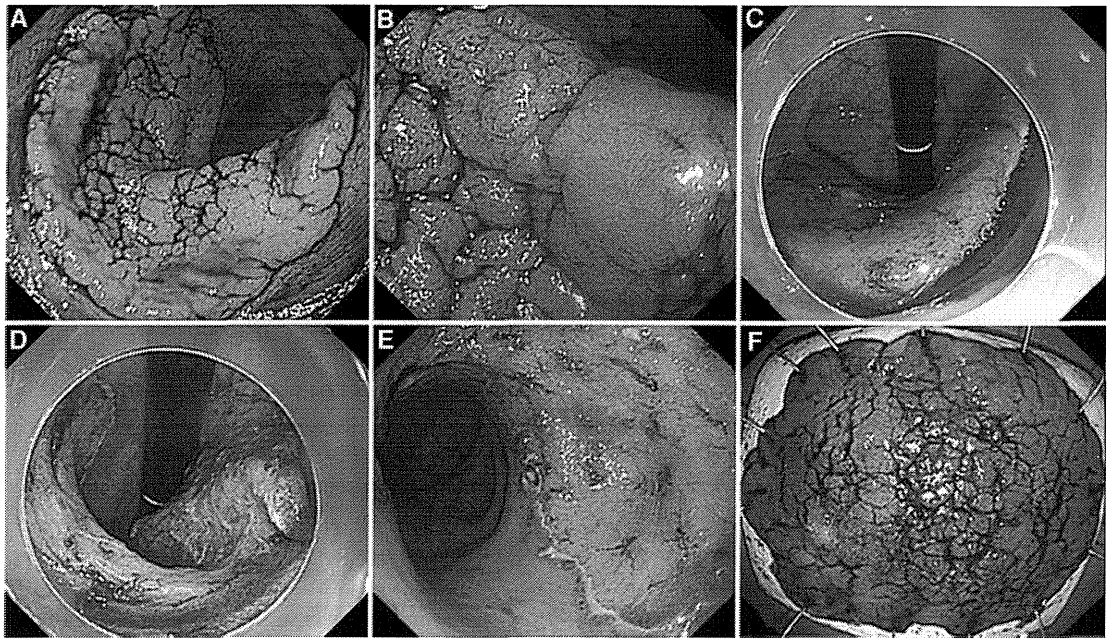


**Fig. 2** Endoscopic submucosal dissection (ESD) procedures, primarily performed using a bipolar needle knife (B-knife) and an insulation-tipped knife (IT knife) with carbon dioxide ($CO_2$) insufflation. **A** Fifty-millimeter laterally spreading tumor nongranular (LST-NG)-type lesion located in the transverse colon. Lesion margins were delineated before ESD using 0.4% indigo-carmine dye spraying. **B** Magnified colonoscopy revealed a noninvasive pattern so the estimated depth of this LST-NG lesion was intramucosal despite its large size. **C** Following injection of Glycerol® (10% glycerol and 5% fructose in normal saline solution) and sodium hyaluronate acid solution into the submucosal layer, a circumferential incision was made using the B-knife. **D** An ESD was then carried out using both the B-knife and IT knife. **E** The ulcer bed is shown here after the successful en bloc resection. **F** The resected specimen was 65 × 50 mm in diameter and histology revealed an intramucosal cancer with a tumor-free margin

snare (10-mm or 25-mm snare master or 20-mm spiral snare; Olympus) as described in previous reports [1–3, 6, 7]. Glyceol® [32] was injected into the sm layer of the lesion with a 23-gauge needle and the lifted lesion was then resected using the snare.

In this study, we distinguished an EMR from an EPMR according to the number of resected pieces as either single or multiple, respectively. An LST-G $\geq$20 mm and $<$40 mm can usually be treated by EPMR rather than ESD with the area including the large nodule resected first followed by the remaining tumor (Fig. 3A–C). After EMR and EPMR, we confirmed whether or not there was any residual tumor using chromomagnification colonoscopy and performed a hot biopsy as necessary for ablative purposes.

Tumor size was estimated by measuring the resected specimen after retrieval for en bloc resected specimens and by comparing the endoscopic observation with the snare size for piecemeal resected specimens.

## Sedation

Midazolam (2 mg/iv) and pentazocin (15 mg/iv) were administered during all ESD procedures. An additional 2 mg midazolam was given as necessary whenever indicated based on the judgment of the colonoscopist. In conventional EMR procedures, midazolam (2 mg iv) was administered to selected patients as determined by the colonoscopist, but only when a patient complained of pain or abdominal distension.

## Histological assessment

All specimens were evaluated after being cut into 2-mm slices and examined microscopically for histological type, depth of invasion, lateral resection margin, and vertical resection margin. Resections were considered tumor free when the lateral and vertical margins of a specimen were both negative for tumor cells independent of its histological features.

A curative resection was achieved when both the lateral and vertical margins of the specimen were free of cancer and there was no sm invasion deeper than 1,000 μm from the muscularis mucosae (sm1), lymphatic invasion, vascular involvement or poorly differentiated component [34]. An adenoma with an unknown lateral margin was also considered to be a curative resection provided that such adenoma met all the other criteria. Histological diagnoses

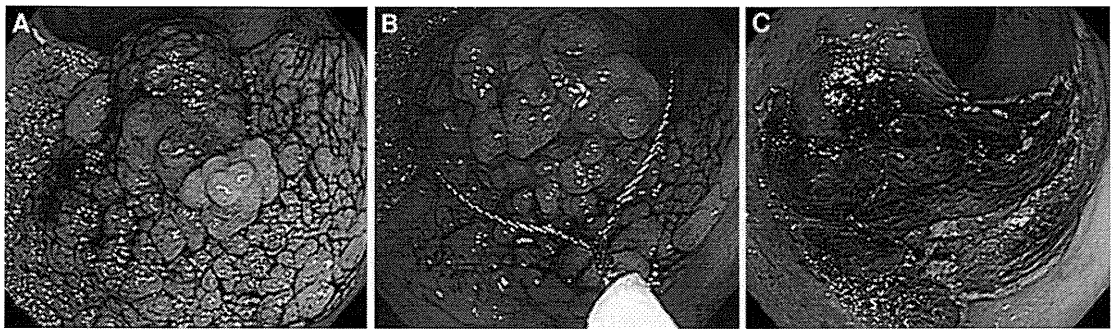


**Fig. 3** Conventional endoscopic mucosal resection (EMR) procedures. Conventional EMRs were usually performed using an inject and cut technique with a single-channel colonoscope and snare. Glycerol® was injected into the submucosa of the lesion with a 23-gauge needle and then the lifted lesion was resected using a round snare. **A** A 35-mm laterally spreading tumor granular (LST-G)-type lesion located in the rectum. **B** An LST-G between 20 and 40 mm can be treated by endoscopic piecemeal mucosal resection (EPMR) rather than ESD with the area including the large nodule resected first followed by the remaining tumor. **C** The ulcer bed after a three-piece resection

were based on the Japanese classification of cancer of the colon and rectum [35] and the Vienna classification [36].

### Follow-up endoscopic care

In assessing for local recurrence or the presence of a residual tumor, we usually repeated colonoscopic examinations at intervals of 6 months for ESD patients because the technique was still relatively new and indicated for large colorectal lesions that had previously been treated surgically. In most cases, we repeated colonoscopic examinations at intervals of 6 months for EPMRs and at 12-month intervals for EMRs with en bloc resections because of an expected lower risk of recurrence [37] with such examinations performed either by the endoscopy staff at NCCH or the patient's previous hospital.

All ESD and EMR patients with sm1 invasion were followed up regularly with annual computed tomography and endoscopic ultrasonography examinations for the detection of lymph-node metastasis. Complete endoscopic follow-up care was available for all 145 lesions in the ESD group and all 228 lesions in the EMR group. Indigo-carmine dye was sprayed on previously resected areas and high-magnification views were obtained in all cases. Recurrent neoplastic disease was identified as type IIIs, IIIL, IV or V pit pattern according to the criteria established by Kudo and Fujii [6, 9, 10, 30–32, 38–41].

### Statistical analysis

All variables in this study are described as mean ± standard deviation (SD). In comparing baseline characteristics between the two groups, we used a *t*-test for continuous variables and a chi-square test for dichotomous variables. All statistical analyses were performed using SAS version 8.0 (SAS Institute Inc., Cary, NC). The *p* values are two-sided and $p < 0.05$ was used to determine statistical significance.

### Ethics

The ethics committee at NCCH approved the study protocol and informed written consent was obtained from all patients in the ESD and EMR groups for each specific colonoscopic treatment and all scheduled follow-up colonoscopy examinations.

## Results

During the study period, 145 lesions were treated with ESD and 228 were treated with conventional EMR (Fig. 1). All 373 lesions were eligible for outcome analysis. Clinical characteristics of the patients in the two groups are presented in Table 2. There were no differences between the two groups in terms of age, gender, endoscopic follow-up frequency or follow-up periods (Tables 2 and 3).

### En-bloc resection rates

In the ESD group, 122 out of 145 lesions (84%) were completely resected en bloc compared with only 74 of 228 lesions (33%) in the EMR group ($p < 0.0001$), although tumor size was significantly larger in the ESD group ($p < 0.0001$) (Table 3).

### Endoscopic characteristics of resected specimens

Regarding macroscopic type, 50% of the EMR group lesions were LST-Gs and 49% of the ESD group lesions were LST-NGs. There were no differences between the two groups in terms of tumor location. The percentage of

**Table 2** Clinical characteristics of patients

| | EMR/EPMR | ESD | *p*-Value |
|---|---|---|---|
| Number of lesions | 228 (74/154) | 145 | |
| Pathology | 77/151 | 45/100 | NS |
| (Adenoma/M-SM1; %) | (34%/66%) | (31%/69%) | NS |
| Macroscopic type | 80/114/34/0 | 5/63/71/6 | |
| (Is/LST-G/LST-NG/recurrence[a]) | (35%/50%/15%/0) | (3%/43%/49%/4%) | <0.0001 |
| Location (Rt/Lt/rectum) | 89/52/110 | 44/28/73 | |
| Tumor size (mean ± SD) | 28 ± 8 mm | 37 ± 14 mm | 0.0006 |
| (range) | (20–95 mm) | (20–140 mm) | |
| Age (mean ± SD; years) | 64 ± 4 | 64 ± 11 | NS |

[a] Recurrence included local recurrence after EMR and residual tumor after incomplete en bloc resection

*EMR* endoscopic mucosal resection; *EPMR* endoscopic piecemeal mucosal resection; *ESD* endoscopic submucosal dissection; *M* intramucosal; *SM* submucosal; *LST-G* laterally spreading tumor granular type; *LST-NG* laterally spreading tumor nongranular type; *Rt* right colon; *Lt* left colon; *SD* standard deviation; *NS* not significant

**Table 3** Clinical outcomes

| | EMR/EPMR | ESD | *p*-Value |
|---|---|---|---|
| Number of lesions | 228 (74/154) | 145 | |
| Endoscopic follow-up times (mean ± SD; number) | 2.4 ± 1.6 | 2.0 ± 1.1 | NS |
| (range) | (1–8) | (1–5) | |
| Endoscopic follow-up periods (mean ± SD; months) | 26 ± 17 | 20 ± 13 | NS |
| (range) | (6–68) | (6–61) | |
| En bloc resection (%) | 74 (33%) | 122 (84%) | <0.0001 |
| Recurrence rate (%) | 33 (14%) | 3 (2%) | <0.0001 |
| En bloc/piecemeal recurrences | 2/31 | 0/3 | |
| Complications | | | |
| Perforation | 3 (1.3%) | 9 (6.2%) | NS |
| Delayed bleeding | 7 (3.1%) | 2 (1.4%) | NS |
| Procedure time (mean ± SD; min) | 29 ± 25 | 108 ± 7 | <0.0001 |
| (range) | (3–120) | (15–360) | |

*EMR* endoscopic mucosal resection; *EPMR* endoscopic piecemeal mucosal resection; *ESD* endoscopic submucosal dissection; *SD* standard deviation; *NS* not significant

carcinomas was 69% in the ESD group and 66% in the EMR group ($p$ = NS) (Tables 2 and 3).

## Local recurrences rates

There were only three cases (2.1%) of local recurrence in the ESD group during a mean endoscopic follow-up period of 20.0 ± 12.9 months (range 6–61 months). In comparison, local recurrence occurred in 14.5% (33/228) of the lesions in the EMR group during a mean endoscopic follow-up period of 25.9 ± 17.0 months (6–68 months). All three recurrences in the ESD group had previously been resected on a piecemeal basis and each recurrence required one additional EMR. Each of these recurrences was diagnosed histologically as a tubular adenoma and curative resections were achieved for all three. The 33 recurrences in the EMR group involved 2/74 (2.7%) en bloc resections and 31/174 (17.8%) piecemeal resections (Table 3). Twenty-six of the 33 EMR recurrent cases were successfully treated by one additional EMR with the other seven cases needing two sessions of repeat EMR. Two EPMRs required surgery because of invasive recurrence (Fig. 4A–F) while a third piecemeal resection also required surgery because of technical difficulty in performing another EMR despite the intramucosal nature of that particular recurrence.

## Duration of recurrence detection

Mean duration of recurrence detection was 6 months (2–18 months) in the EMR group and 6 months (4–6 months) in the ESD group (Table 3).

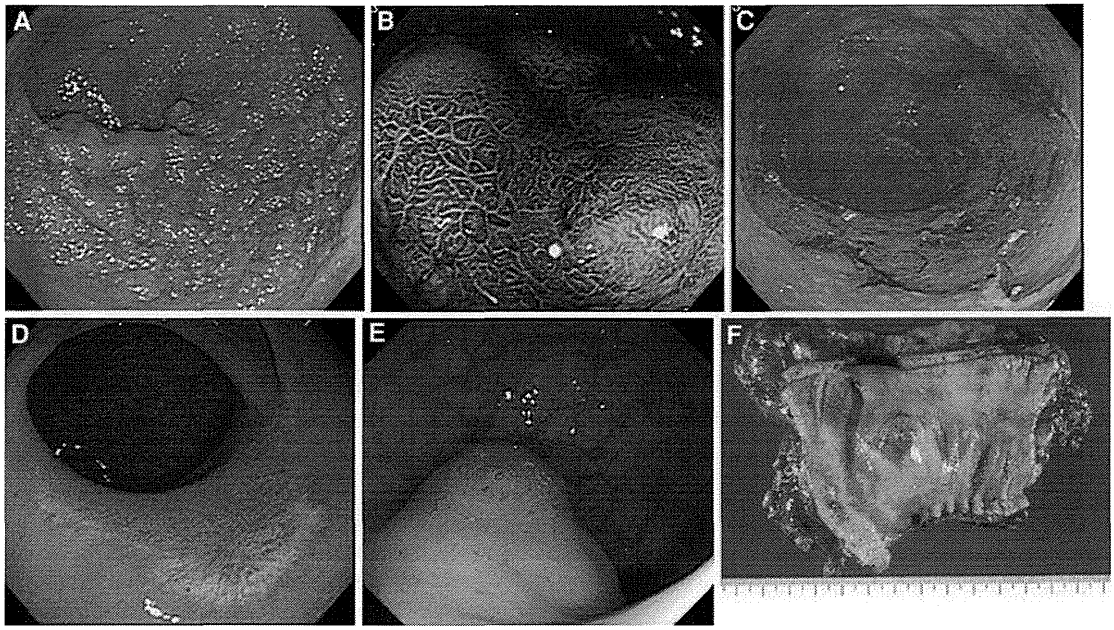


**Fig. 4** **A** This case originally involved a large LST-G lesion >3/4 in circumference. **B** Magnified colonoscopy using 0.05% crystal violet staining revealed a noninvasive pattern on the large nodule. **C** An EPMR consisting of more than ten pieces finally resected the entire lesion. Histology revealed an intramucosal carcinoma without any evidence of lymphovascular invasion or a poorly differentiated component so we followed this patient closely without surgery. **D** The third follow-up colonoscopy after 18 months revealed no recurrence. **E** A fourth follow-up was performed 1 year later, at which time a submucosal tumor-like recurrence was found 1 cm from the original EPMR scar. **F** Surgery was performed on this lesion and histology revealed the recurrence of an invasive cancer

### Early and late complications

Perforations occurred in 9 out of 145 patients (6.2%) in the ESD group, which was higher compared with the perforation rate of 1.3% (3/228) in the EMR group ($p$ = NS). None of the 12 perforations was delayed and all of them were successfully treated endoscopically using endoclips and managed conservatively.

Minor delayed bleeding occurred in two patients (1.4%) in the ESD group and seven (3.1%) patients in the EMR group ($p$ = NS), but all nine cases were successfully managed conservatively using endoclips with no blood transfusions or additional procedures necessary (Table 3).

### Procedure times

The procedure time for ESDs was 108 ± 71 min (15–360 min) compared with 29 ± 25 min (3–120 min) for EMRs, resulting in a significantly shorter procedure time for the EMR group ($p < 0.0001$) (Table 3).

## Discussion

This study is, to the best of our knowledge, the first to compare clinical outcomes for colorectal ESD with EMR/EPMR including mid-term follow-up.

For many years, conventional EMR and surgery were the only available treatments for large colorectal tumors, even those detected at an early stage. Conventional EMRs usually resulted in EPMRs particularly for large LSTs ≥20 mm with reports of local recurrence rates ranging from 7.4% to 17% [8, 12, 32]. Most of those recurrences, however, received repeated endoscopic treatment with excellent results regarding preservation of the colorectum [32].

In our series, the introduction of ESD enabled us to effectively treat large colorectal tumors that were LST-NGs and carcinomas, resulting in higher en bloc resection and curability rates compared with conventional EMR. EPMR also was effective in treating many LST-Gs ≥20 mm, with only three cases requiring surgery after such piecemeal resections, including two invasive recurrences cases. Those two cases were originally diagnosed histologically as intramucosal carcinomas without lymphatic or vascular invasion, but both recurrences consisted of invasive carcinomas. We suspect that each case may have originally involved either sm invasion or lymphatic invasion that was not diagnosed histologically because of the increased difficulty in assessing a piecemeal resection. Based on our results, therefore, EPMRs must be performed carefully and close follow-up is required in the event that additional treatment becomes necessary because accurate histological evaluation can be difficult or impossible in

such cases. As an alternative, greater consideration should be given to either ESD or laparoscopic surgery rather than EPMR.

Conventional EMRs in this study had an overall local recurrence rate that was similar to in previous reports [12, 33], as en bloc resection cases resulted in a low recurrence rate of 3%, but piecemeal resections had a considerably higher recurrence rate of 20%. In contrast, ESDs resulted in a significantly higher en bloc resection rate and, consequently, a significantly lower recurrence rate. In those ESDs in which en bloc resections were not achieved, however, the local recurrence rate was approximately 13%, which was much closer to the local recurrence rate for EPMRs. According to our findings, EPMR resulted in a higher recurrence rate compared with ESD, although EPMR produced results similar to those of ESD in relation to preservation of the colorectum.

In this study, we conducted follow-up examinations on patients 6 month after EPMRs and 1 year after EMR en bloc resections, regardless of the lateral margin findings. This was based on our preliminary data [33] indicating that EPMR recurrences were more frequent compared with EMR en bloc resection recurrences and most such EPMR recurrences occurred within 6 months. This current study once again confirmed that most EPMR recurrences were detected after the first 6 months, so such recurrences could continue to be successfully treated endoscopically, supporting the propriety of our follow-up program after EPMR.

As for complications, the perforation rate in the ESD group was 6.2%, which was considerably higher than the 1.3% perforation rate in the EMR group, although there was no statistical difference between the two groups. In other reported series, the perforation rates for colorectal ESDs [8, 27, 28] and EMRs [42] ranged from 1.4% (1/71) to 5.5% (11/200) and 0.31% to 0.93%, respectively, which were similar to our results. The target lesions for ESD in this study, however, were large LSTs that would have been treated by surgery in the past because of the technical difficulty [43]. In fact, the mean tumor size was significantly larger in the ESD group compared with the EMR group so conventional EMRs performed on such lesions undoubtedly would have resulted in a higher complication rate for the EMR group.

All perforation cases were successfully treated conservatively without surgery by endoscopic clipping. As a result, the perforation rate of 6.2% in the ESD group was considered to be acceptable, although further instrument improvements and technique refinements will both be necessary to reduce the perforation rate. The delayed bleeding rate was relatively low in both groups, but particularly in the ESD group, probably because small vessels were coagulated during the ESD procedure.

Considering the additional procedure time and increased cost of ESD devices, it would be difficult to standardize the colorectal ESD procedure on a widespread basis at the present time. We currently select lesions with more serious indications for colorectal ESD that would otherwise be treated surgically. Such ESD patients usually are discharged from the hospital sooner than if surgery had been performed, resulting in reduced medical costs.

Finally, the long-term efficacy of colorectal ESD needs to be established by evaluating an extended follow-up period, although ESD certainly appears to be a feasible alternative to conventional EMR, particularly for certain kinds of colorectal cancers. This study was not a randomized controlled trial, however, and eligibility criteria for the two endoscopy procedures were sometimes unclear for different kinds of lesions. It will be necessary, therefore, to prospectively assess the clinical outcome comparison between ESD and EMR for large colorectal tumors in the future. Another limitation of this study that may have been a source of bias was the exclusion of 40% of the total EMR/EPMR cases from our analysis because follow-up colonoscopy examinations were not carried out at NCCH or could not be ascertained by us.

In conclusion, ESD was selected more often for treating large colorectal tumors because it provided higher en bloc resection and curability rates compared with EMR despite the longer procedure time and higher perforation rate associated with ESD. All ESD perforations, however, could be successfully managed by conservative endoscopic treatment. EMR effectively treated many large colorectal tumors, and only three cases required surgery after EPMRs; such procedures should be carefully performed because it can be more difficult and occasionally impossible to make an accurate histological evaluation, meaning that close follow-up is required in the event that additional treatment is necessary in such cases.

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# Assessment of Likelihood of Submucosal Invasion in Non-Polypoid Colorectal Neoplasms

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**KEYWORDS**

- Non-polypoid colorectal neoplasm • Submucosal cancer
- Lymph node metastasis • Endoscopic diagnosis
- Magnifying chromoendoscopy

Endoscopic mucosal resection (EMR) is indicated to treat intramucosal colorectal carcinoma because the risk of lymph node metastasis is nil.[1,2] Surgery is indicated to treat submucosal invasive cancers (cancer cells invading through the muscularis mucosa into the submucosal layer but not extending into the muscularis propria) because of the 6% to 12% risk of lymph node metastasis.[3–7] However, there is increasing evidence to suggest that lesions with submucosal invasion lower than 1000 μm, without lymphovascular invasion and without poor differentiation, also have a minimal risk of lymph node metastasis[8] and can be cured by EMR alone. It is therefore important to be able to distinguish neoplasms that are candidates for EMR from those that will require surgery, because EMR of lesions containing massive submucosal invasive cancer is associated with the risk of bleeding and perforation and is unlikely to be curative.

Current endoscopes have high-resolution imaging that provides clear, vivid, and detailed features of the detected lesions. When combined with image enhancement, high-magnification endoscopy can provide a detailed analysis of the morphologic architecture of mucosal crypt orifices (ie, pit pattern) in a simple and quick manner.[9,10] As such, magnifying chromoendoscopy has been shown to be effective for the differential

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diagnosis between colorectal neoplastic and non-neoplastic lesions and determination of the depth invasion of colorectal cancers. The authors highlight methods to assess depth of invasion of non-polypoid colorectal cancers based on a review of the literature and our experience at National Cancer Center Hospital in Japan.

## IMPORTANCE OF ESTIMATION OF SUBMUCOSAL INVASION

In Japan, findings of deep submucosal invasion ($\geq$1000 μm), and/or lymphovascular invasion, and/or poorly differentiated adenocarcinoma in the histopathology of an EMR specimen would lead to consideration for surgery. Though lymphovascular invasion and poorly differentiated adenocarcinoma components are impossible to predict before resection, the vertical depth of invasion of submucosal cancers can be estimated based on the morphologic appearance at the time of endoscopy.

However, estimation of submucosal invasion requires more than the measurement of the lesion size. Small colorectal neoplasms are historically believed to have a lower malignancy potential than large ones, and several authors have reported that the malignant potential of early colorectal cancer increases with size.[11–13] Although this observation may be true for adenomatous lesions, the data for submucosally invasive carcinomas are conflicting. In the authors' own large study involving 583 lesions, they found that that small submucosal cancers ($\leq$10 mm, n = 120) had a similarly aggressive behavior and malignant potential as the larger ones (>10mm, n = 463); the risks of lymph node metastasis were similar (small: 11.2%, large: 12.1%, $P$ = .85), lymphovascular invasion (small: 21.7%, large: 27%, $P$ = .23), and poorly differentiated adenocarcinoma components (small: 10%, large: 17.1%, $P$ = .06).[7] They also described that small submucosal cancers were more likely to have non-polypoid growth (NPG) type[14] than the larger lesions (68.3% vs 46.0%, $P$<.0001). In this retrospective study, the rate of EMR used as an initial treatment was 33.4% (195/583). EMR was more often used to resect the small lesion rather than the large lesion group (51.6% vs 28.7%, $P$<.0001). However, they were surprised to find that there were no differences in the positive rate of cut margins in both groups (17.7% vs 19.5%, $P$ = .81). This result implies that EMR should not be easily applied to small colorectal lesions when they appear to be submucosally invasive because of its risk of complication and the concept of no-touch isolation.[15]

## ESTIMATION OF SUBMUCOSAL INVASION USING BARIUM ENEMA, ENDOSCOPIC ULTRASONOGRAPHY, AND NONLIFTING SIGN

### *Barium Enema*

The superiority of barium enema over colonoscopy is summarized by Tsuji and colleagues[16] as follows: (1) Barium enema is able to describe the shape of the lesion that is difficult for colonoscopy to observe because of its location. (2) In the case of a large lesion in which it is difficult to endoscopically observe the whole lesion, barium enema can describe the entire shape of the lesion and obtain information on the oral side more easily. (3) The size and location of lesions can be assessed more objectively. (4) The degree of deformity of the lateral view enables the clinician to diagnose the depth of invasion more easily.

The authors retrospectively compared the diagnostic accuracy of colonoscopy and barium enema for submucosal colorectal cancers at 2 National Cancer Centers (Tokyo, Kashiwa) in 2001.[17] One hundred eighty-six (polypoid [Ip, Is]: 117, non-polypoid [IIa, IIa+IIc, IIc, laterally spreading tumor (LST)]: 69) lesions were examined in this study, and the authors investigated the accuracy rate of the lesion's depth by 2 modalities (**Fig. 1**). The colonoscopic accuracy rate was superior to that of the barium enema study